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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,830	01/08/2001	Sydney Brenner	5525-0046.30	6856

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,830	BRENNER ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6 and 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03 August 2006 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3, 4, 6, and 19-21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. As presently worded, claim 1 calls for the generation of a 'repertoire of oligonucleotide tags having the predetermined length," however, the aspect of there being a 'repertoire" speaks to there being a plurality of lengths, not just one. Further, the method fairly encompasses the use or inclusion of linkers of virtually any length, which can and would alter the length of the oligonucleotide tags. Accordingly, it is not clear how "the predetermined length" is achieved across the board when reaction conditions are not fixed.

5. Claims 3, 4, 6, and 19-21, which depend from claim 1, fail to overcome this issue and are similarly rejected.

6. Claim 1, last step, requires "repeating steps (b) through (e) until a repertoire of oligonucleotide tags having the predetermined length is formed." It is noted that step (e) requires "amplifying the elongated oligonucleotide tag precursors in said first vector." (Emphasis added.) As presently worded, it appears that there is at least one method step missing as the ultimate step is a never-ending amplification step which only would produce more of a "precursor," not the required "repertoire of oligonucleotide tags."

7. Claims 3, 4, 6, and 19-21, which depend from claim 1, fail to overcome this issue and are similarly rejected.

8. Claim 15 is confusing as to how the nucleotides that make up the various words differ from the nucleotide(s) ("N") that fall between words, regardless of length of the word (e.g., claim 16). It is also not clear if these intervening nucleotides care to be "minimally cross-hybridizing" or not, and if they are, then to what is their ability to hybridize being related.

9. Claims 16-18, which depend from claim 15, fail to overcome this issue and are similarly rejected.

10. Claims 1, 3, 4, 6, and 15-21 are indefinite with respect to what constitutes "minimally cross-hybridizing' when the oligonucleotide tags are single stranded and there is no complement upon which to make a determination of mismatches being present. It is noted further that the claims do not require the "oligonucleotide tags" to be double stranded. If such were added to the claims, this issue may be resolved.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 3, 4, 6, and 15-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary,

The quantity of experimentation needed is great, on the order of several man-years with little if any reasonable expectation of success in identifying useful nucleic acids.

The amount of direction or guidance presented,

The amount of guidance provided is extremely limited. The specification (Sequence Listing of 24 October 2003) sets forth 39 nucleotides, which are labeled as artificial sequence, adaptor, or vector. While the claims encompass a virtually limitless number of embodiments, the disclosure of only several representative oligonucleotide tags does not fully enable the full scope of making said oligonucleotide tags, nor fully enable the use of the genus of said tags. In support of this position attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.
>
> ***
>
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

The presence or absence of working examples,

The specification provides the following examples:

a. Example 1, "Repertoire Synthesis by Repeated Cycles of Cleavage, Self-Selection, Ligation, and Amplification," pages 14-16;

b. Example 2, "Repertoire Synthesis by Convergent Assembly of Error-free Oligonucleotide Tag Precursors," pages 16-18;

c. Example 3, "Construction of an Eight-Word Tag Library," pages 18-24.

The nature of the invention,

The invention relates to nucleic acids that may range form 18 to 60 nucleotides in length (claims 1, 3, 4, 6, and 19-21), and from 30-1400 nucleotides in length (claims 15-18), which comprise numerous mismatches between otherwise complementary strands. No specific property, other than presence of mismatches, is required.

The state of the prior art,

The state of the prior art has developed to the point where novel nucleic acids, such as those associated with expressed sequence tags, are being identified yet no known function of the nucleic acid, or possible encoded protein is known.

The predictability or unpredictability of the art, and

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The breadth of the claims.

The claims encompass the production of a virtually limitless number of oligonucleotide tags of dubious value.

Claim 1, last step, requires "repeating steps (b) through (e) until a repertoire of oligonucleotide tags having the predetermined length is formed." It is noted that step (e) requires "amplifying the elongated oligonucleotide tag precursors in said first vector." (Emphasis added.) As presently worded, it appears that there is at least one method step missing as the ultimate step is a never-ending amplification step which only would produce more of a "precursor," not the required "repertoire of oligonucleotide tags." Accordingly, the specification does not enable the production of "oligonucleotide tags" when such is never realized.

13. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

14. Claims 1, 3, 4, 6, and 19-21 are all drawn to a method of synthesizing a repertoire of oligonucleotide tags. Claims 15-18 are drawn to said set of oligonucleotide tags. The specification has not been found to set forth a specific and substantial utility for the product and a review of the disclosure fails to find where the resultant and clamed product, when used, would in turn meet the utility requirements. Specifically, it is not enough that one can synthesize, or claim outright, a "tag" that could be used to determine if a complementary sequence is present, e.g., an expressed sequence tag or EST, a sequence for which no known utility exists. While the tags can be used to determine if a complementary sequence exists, all nucleic acids can be used in such a manner. While one may elect for that which exhibits less cross-hybridization, the intended target, even if unique, must have a specific and substantial utility. Simply determining its existence does not suffice.

15. The situation at hand is analogous to that of *In re Fisher* (CAFC, 04-1465, decided 07 September 2005). In *Fisher* the disclosure provided five ESTs and assertions as to their potential utility. Here, applicant is claiming a method of producing "tags" and the "tags" per se. Like *Fisher*, no evidence has been presented that the product of the claimed method or the product outright, does in fact have any of the alleged utilities. Further, the aspect of finding complementary sequences (which could be an EST) is not considered to be a substantial utility as the utility requirement is not satisfied for like the ESTs of *Fisher*, the product, even it had been produced/found, would be at best the subject of further research and development so to determine if it does in fact have any real value. In view of the clear need for the product of the claimed invention to have utility, and no convincing showing has been made in this regard as to

its satisfaction, no specific, substantial, and credible utility exists in readily available form a the time of filing.

16. Claims 1, 3, 4, 6, and 15-21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to argument

At page 9, bridging to page 10 of the response of 03 August 2006, argument is presented that: "'Such repertoires [of tags] permit tagging and sorting of molecules with a much higher degree of specificity than ordinary oligonucleotides' (page 2, lines 29-30)."

The preceding argument has been fully considered and has not been found persuasive, as the argument is conclusory in nature and void of any factual underpinning. It is noted that no example shows that any oligonucleotide tag, produced by the claimed method, has been used in any method, much less be used in the aforementioned method and then found to yield superior results. It matters not whether the claim is drawn to a product or process; the claim must be drawn to an invention that satisfies the utility requirements as set forth under 35 USC 101 and as further developed in the Utility Guidelines. In support of this position, attention is directed to *Brenner, Comr. Pats. v. Manso*n, 148 USPQ 689 (US SupCt 1966):

> Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, 22

> without compensating benefit to the public. The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> * * *
>
> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product. 24 That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.
> This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of the invention of something "useful," or that we are blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

For the above reasons, and in the absence of convincing evidence to the contrary, claims 1, 3, 4, 6, and 15-21 are rejected under 35 USC 101, and 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1, 3, 4, 6, and 15-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/41011 (Brenner et al.) in view of US Patent 5,827,816 (Theofan et al.).

21. Brenner et al., disclose a method of synthesizing oligonucleotide tags. Table 1, page 9, sets forth various lengths of the words that the tag is to comprise. Page 11, last paragraph, discloses that a preferred embodiment is one where the minimally cross-hybridizing sets of oligonucleotides are made up of subunits (words) of for four natural nucleotides.

22. Brenner et al., page 13, teaches of the presence of complementary strands being present.

23. Page 14, fourth paragraph, teaches that the oligonucleotides may range form 12 to 60 nucleotides or basepairs.

24. Brenner et al., page 23, penultimate paragraph, teaches manipulating the oligonucleotides via standard molecular biology techniques. The use of restriction endonucleases, including Type IIs (Fok I), is disclosed at page 24.

25. Brenner et al., page 35, discloses excising the insert from a vector.

26. Brenner et al., page 44 (Example 2), discloses using a 36mer tag that was comprised of 9 words, which are comprised of 4 nucleotides each.

27. Brenner et al., has not been found to disclose production of the oligonucleotide tags in a vector, such as through cell culture.

28. Theofan et al., column 8, discloses excising inserts from one plasmid, ligating multiple inserts, and reinserting the cleaved inserts into a plasmid (applicant's vector), and then amplifying the newly assembled vector/insert construct.

29. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the use of a vector for insert amplification as disclosed by Theofan et al., with the method of producing oligonucleotide tags, as disclosed by Brenner et al., as Theofan et al., teaches explicitly of combining multiple inserts (applicant's multiple words) so to form a new oligonucleotide tag of a predetermined length, and to then amplify same in a vector as such is well known and predictable in the art. One would have found further motivation as Brenner teaches explicitly of taking advantage of molecular biology techniques.

30. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1, 3, 4, 6, and 15-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/41011 (Brenner et al.) in view of US Patent 5,827,816 (Theofan et al.).

Conclusion

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS